Similar Efficacy of Lirentelimab in Patients With New vs Established Diagnoses of Eosinophilic Gastritis and/or Duodenitis in a Randomized Trial

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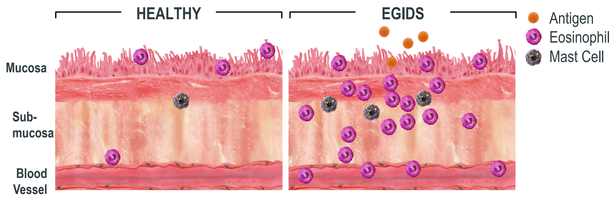
BACKGROUND

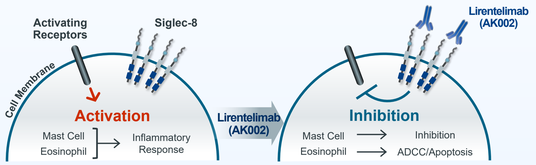
- Pathologic accumulation and over-activation of eosinophils and mast cells are implicated in multiple chronic inflammatory diseases in the gastrointestinal (GI) tract including eosinophilic esophagitis (EoE), gastritis (EG), duodenitis (EoD), and colitis—collectively termed eosinophilic gastrointestinal diseases (EGIDs)[1,2]
- Patients with EGIDs have decreased quality of life due to chronic debilitating and often nonspecific symptoms such as dysphagia, abdominal pain, bloating, nausea, vomiting, and diarrhea[3]

Figure 1. Pathogenesis of EGIDs



- EG and/or EoD are thought to affect 45,000–50,000 patients in the US, although this is believed to be an underestimation—there is evidence that EG and/or EoD are as common as inflammatory bowel diseases (IBD)[4,5]
- Current treatment options, such as diet restriction and corticosteroids, have limited efficacy and/or are inappropriate for chronic use
- There is a significant unmet need for novel therapies

Figure 2. Lirentelimab (AK002) Proposed Mechanism of Action



- Siglec-8 is an inhibitory receptor selectively expressed on mature human eosinophils and mast cells and is a novel target for the treatment of EGIDs
- Lirentelimab (AK002), an investigational medicine, is a humanized, non-fucosylated IgG1 monoclonal Siglec-8 antibody*
- Engagement of Siglec-8 receptor by lirentelimab triggers:
  - Antibody dependent cell mediated cytotoxicity (ADCC, blood) and apoptosis (tissue) of eosinophils
  - Inhibition of mature mast cells in tissue
- Results from the phase 2 study of lirentelimab in patients with EG and/or EoD, ENIGMA, have been published; in this study, 13/65 (20%) subjects did not have previous diagnoses of EG or EoD[6]
- Here we characterize and compare long-term outcomes of patients with new diagnoses of EG and/or EoD with patients with previously established diagnoses

OBJECTIVES

- Evaluate the discovery rate of EG and/or EoD among previously undiagnosed patients with chronic non-specific GI symptoms enrolled in ENIGMA
- Describe patients with new or established diagnoses of EG and/or EoD
- Compare responses to lirentelimab in patients with new vs established diagnoses of EG and/or EoD

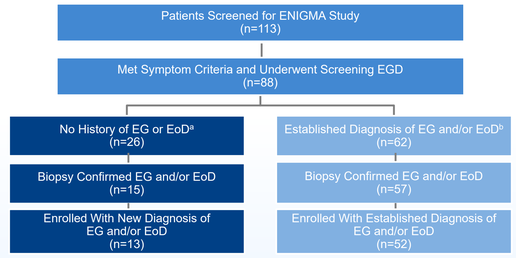
METHODS

- ENIGMA was a phase 2 multi-center, randomized, double-blind, placebo-controlled study of lirentelimab in 65 patients with EG and/or EoD
  - Patients were eligible for the study if they had:
    - Active moderate–severe symptoms[a] based on the daily EG/EoD-SQ© questionnaire, which assesses 8 symptoms (each on a scale of 0–10) to produce a Total Symptom Score (TSS; range, 0–80)
    - Confirmed EG and/or EoD, based on 8 biopsies from the stomach (≥30 eos/hpf in 5 hpfs) and/or 4 from the duodenum (≥30 eos/hpf in 3 hpfs)
  - Patients were randomly assigned (1:1:1) to groups that received 4 monthly doses of placebo, a low-dose lirentelimab regimen (first dose 0.3 mg/kg, last 3 doses 1.0 mg/kg), or a high-dose lirentelimab regimen (0.3 mg/kg, 1.0 mg/kg, and last 2 doses 3.0 mg/kg)
- 58 of 59 eligible patients who completed the ENIGMA study chose to enter the OLE study and receive lirentelimab
  - Up to 26 monthly lirentelimab infusions every 28 days, titrated to 3.0 mg/kg
  - Upper endoscopy with biopsy collection on day 323 after entering ENIGMA
  - Patients assessed daily with the EG/EoD Symptom Questionnaire
  - ENIGMA OLE is ongoing; data presented from July 7, 2021
- In this supplemental analysis, we analyzed subgroups of patients with new vs previously established diagnoses of EG and/or EoD, comparing baseline characteristics, medical histories, and responses to treatment

a Patient-reported outcome entry criteria: average weekly score over ≥2 weeks of ≥3 for either abdominal pain, diarrhea and/or nausea

RESULTS

Figure 3. ENIGMA Screening Indicated Underdiagnosis of EG and/or EoD



a General GI practices and professional GI research centers; n=51 entered screening
b Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) sites; n=62 entered screening

- 113 patients entered screening, 88 met the criteria for moderate–severe symptoms and underwent screening endoscopy with biopsy, 72 met histologic criteria for EG and/or EoD, and 65 were randomly assigned to groups given lirentelimab (low-dose, n=22 or high-dose, n=21) or placebo (n=22)
- 51 patients entered screening without an established diagnosis of EG or EoD; 15 patients (29%) were diagnosed with EG and/or EoD in ENIGMA

Table 1. Characteristics of Patients With New vs Previous Diagnosis of EG and/or EoD

Patients with EG and/or EoD (n=72)		New Diagnosis (n=15)	Established Diagnosis (n=57)
Age (years), mean (range)		48 (20–74)	40 (18–68)
Female		67% (10)	58% (33)
White		93% (14)	91% (52)
Immunoglobulin E (IU/mL), mean (range)		127 (10–898)	665 (10–7240)
Absolute eosinophil count /µL	mean (range)	133 (30–340)	791 (40–4900)
	% (n) with < 250	87% (13)	25% (14)
	% (n) with ≥ 250	13% (2)	75% (43)
Gastrointestinal eosinophils/hpf, mean (range)		54 (36–117)	92 (33–300)
Gastrointestinal mast cells/hpf, mean (range)		51 (35–84)	67 (20–139)
TSS (range, 0-80), mean		31.7	31.3
History of	EoE	27% (4)	61% (35)
	asthma	40% (6)	39% (22)
	atopic dermatitis	20% (3)	18% (10)

Table 2. GI Disorders in Patients With New vs Previous Diagnosis of EG and/or EoD

Number (%) of subjects with	Met Symptom Criteria n=88	Met EG/EoD Histologic Criteria n=72	New Diagnosis n=15	Established Diagnosis n=57
Functional abdominal pain	7 (8%)	7 (10%)	0 (0%)	7 (12%)
Functional constipation	10 (11%)	8 (11%)	3 (20%)	5 (9%)
Functional diarrhea	20 (23%)	18 (25%)	7 (47%)	11 (19%)
Irritable bowel syndrome (IBS)	3 (3%)	3 (4%)	1 (7%)	2 (4%)
Gastroesophageal/acid reflux (GER/GERD)	26 (30%)	24 (33%)	8 (53%)	16 (28%)
Peptic ulcer	9 (10%)	9 (13%)	1 (7%)	8 (14%)
Chronic gastritis or duodenitis	6 (7%)	4 (6%)	4 (27%)	0 (0%)
One or more of the above	48 (55%)	43 (60%)	13 (87%)	30 (53%)

Figure 4. GI Symptoms in Patients with New vs Previous Diagnosis of EG and/or EoD

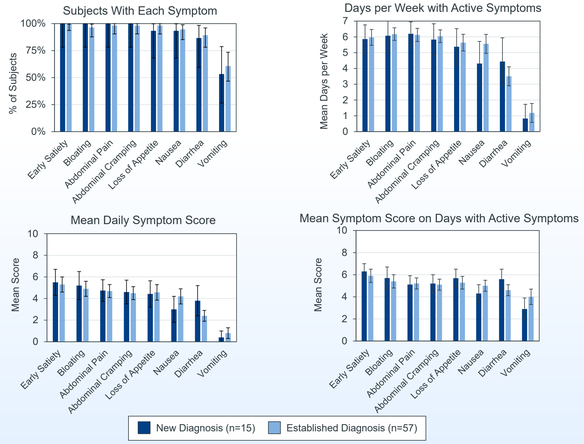
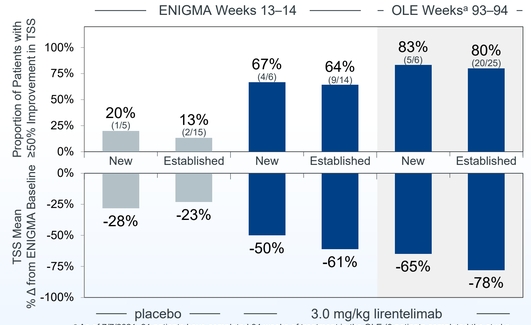


Figure 5. TSS Responses in Patients With New vs Previous Diagnosis of EG and/or EoD



[a] As of 7/7/2021, 31 patients have completed 94 weeks of treatment in the OLE (8 patients completed the study; 21 discontinued; [none due to drug related adverse events])

- Patients receiving lirentelimab had a sustained symptom responses through 94 weeks of treatment
- No significant difference was observed between patients with new vs established diagnosis of EG and/or EoD

Safety Summary

- In ENIGMA and the OLE, the most common adverse event (AE) was mild to moderate infusion-related reactions (IRRs)[a]; mostly occurred on first infusion, greatly reduced or did not occur on subsequent infusions
- ENIGMA safety results have been published[6]
  - One drug-related serious adverse (SAE) event in ENIGMA, an IRR which recovered within 24 hours with no further sequelae
- In the OLE
  - AEs that occurred in >10% of patients were IRR, headache, nasopharyngitis, and nausea
  - No drug-related SAEs in the OLE study as of 7/7/2021

a Most IRRs were flushing, feeling of warmth, headache, nausea, and/or dizziness

CONCLUSIONS/DISCUSSION

- 15 of 51 (29%) of patients entering ENIGMA without an established diagnosis of EG or EoD were found to have EG and/or EoD
- No significant difference in symptom response observed in patients with new vs established diagnoses of EG and/or EoD (based on TSS) to lirentelimab in ENIGMA and the OLE
- Patients receiving lirentelimab in the OLE had further improvement, through week 94, in symptoms
- EG and/or EoD appear to be more common than previously reported
- Patients with chronic, moderate–severe unexplained GI symptoms should undergo upper endoscopy with systematic collection of gastric and duodenal biopsies to identify those with EG and/or EoD
- Lirentelimab was generally well tolerated; ENIGMA and OLE results help characterize its safety profile in the studied patient populations

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*Lirentelimab is an investigational medicine, its efficacy and safety profile have not been established, and it has not been approved by the FDA

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